

Neuroimaging and Resilience Factors - Staging of the At-risk Mental State?

Renata Smieskova^{1,2,*}, Paolo Fusar-Poli³, Anita Riecher-Rössler¹ and Stefan Borgwardt^{1,2,3}

¹Department of Psychiatry, University of Basel, 4031 Basel, Switzerland, ²Medical Image Analysis Centre, University of Basel, Switzerland, ³King's College London, Institute of Psychiatry, Department of Psychosis Studies, De Crespigny Park, London SE5 8AF, United Kingdom

Abstract: Over the past decade, vulnerability- and psychosis-associated structural and functional brain abnormalities in a population at high clinical risk to develop psychosis were intensively studied. We reviewed the results from studies comparing at-risk mental state (ARMS) individuals with and without subsequent transition to psychosis. Additionally, we introduced a new concept of splitting ARMS population according to the duration of the psychosis risk syndrome and their probability to develop psychosis. Studying the ARMS individuals still vulnerable to psychosis but with lower risk to transit can disclose the possible protective – resilience factors or characteristics. Resilience, understood as ability to recover from change, can be thus applied in the early intervention for high clinical risk for psychosis individuals.

Keywords: At-risk mental state (ARMS), transition, psychosis, resilience, magnetic resonance imaging (MRI).

1. THE PRODROMAL STAGE OF PSYCHOSIS

The research in the prodromal stages of serious physical diseases, e.g. cardiovascular and oncological diseases, has exponentially progressed. Similarly, over the last decades early clinical detection and intervention in patients with psychoses have become widespread. Psychosis seems to be preventable or at least successfully treatable in the early stages before frank psychosis breakdown [1, 2]. Early detection services worldwide [3-5] identify individuals, who are experiencing prodromal symptoms characterized by attenuated psychotic symptoms, or brief limited psychotic symptoms or a decline in social and/or occupational functioning. They are broadly termed as having a clinical high-risk or an ‘at risk mental state’ (ARMS) (for review see [6]), more recently as the ‘Psychosis Risk Syndrome’ [7]. Research in early and prodromal phases of the illness may provide important findings on etiology that are not confounded by medication and/or chronicity related effects.

The developing psychosis is understood as a continuum with early mild clinical signs [6, 8-10]. A high-risk state of psychosis may be a consequence of a genetic predisposition [11] and/or gene-neurodevelopmental interaction [12-14] and/or other stress factors [15] leading to the increased clinical risk for psychosis. Around 15-40% [2, 3, 5, 13, 16] of these high-risk individuals go on to develop psychosis with more severe symptoms and some of them continue to a serious chronic disease. Research has attempted to identify definitive markers that distinguish those, who go on to develop psychosis from those, who do not. However, it is difficult to identify the individuals, who will later develop psychosis solely on clinical or symptomatic grounds. Therefore, we are facing the need to additionally characterize vulnerability- and resilience-associated neurobiological markers. Neuroimaging methods help to clarify the mechanisms underlying psychosis, as the same individuals can be studied before and after the onset of frank psychosis, often with only minimal confounding effects of the previous treatment.

The term ‘at-risk mental state’ (ARMS) has been suggested as a replacement of the term ‘prodromal’, to delineate a subthreshold syndrome that confers high – but not inevitable – risk for development of psychotic disorder in the near future [5]. The ARMS is defined according to the PACE (Personal Assessment and Crisis Evaluation Clinic, Melbourne) criteria and requires individuals to

present a) attenuated positive psychotic or b) brief limited intermittent symptoms that do not reach the threshold of frank psychosis or c) functional decline and genetic risk [3, 16, 17]. These psychopathological symptoms are often associated with negative symptoms [3, 9] and subtle cognitive deficits [3, 18-20]. Furthermore, neurofunctional deficits may be associated with transition to psychosis and thus can be seen as vulnerability markers for developing frank psychosis [3, 21].

2. NEUROIMAGING FINDINGS IN PSYCHOSIS

Postmortem [22, 23] as well as neuroimaging studies described brain structural deficits of patients suffering from psychosis [24]. The most replicated and pronounced findings are increase of ventricular volumes and reduction of total gray matter, white matter and whole brain volume [25-27]. Meta-analyses of voxel based morphometry studies in schizophrenia have shown additional regional gray matter volume (GMV) reduction in the anterior cingulate, insula, medial prefrontal and temporal cortex, in the thalamic and other subcortical regions [28-31]. In first-episode patients, hippocampal, thalamic, insular and cingulate cortex reductions are involved [32]. More extensive reductions in medial and dorsolateral prefrontal cortex and in the superior temporal gyrus have been observed in chronic schizophrenia [32]. A number of confounding factors may influence the heterogeneity across imaging findings [33, 34], in particular antipsychotic medication may play a prominent role [35]. However, conflicting results across studies prevent applicability of imaging methods in clinical psychiatry. Some of the brain structural abnormalities have been characterized as trait factors, known to be present in relatives of schizophrenia patients [36, 37]. Other disease-related abnormalities seem to be state markers, i.e. markers of very early stages (high clinical risk for psychosis), of transition to full-blown psychosis or of chronic disease. Pantelis *et al.* described acceleration of gray matter reduction specifically in prefrontal region in first-episode patients, prodromal patients and high-risk individuals [12]. Not only abnormalities in the brain network, but also reduced connectivity between distinct brain regions appear to apply across all stages of schizophrenia [38].

On the other hand, several neurofunctional abnormalities have been described in patients suffering from psychosis. Executive function impairments including working memory (WM) [39-47], spatial memory and verbal fluency deficits [48-55], and reward and salience processing anomalies [56-59] are pronounced cognitive features found in schizophrenia. However, the relation of physiological and clinical variables (positive, negative symptoms) is

*Address correspondence to this author at the Department of Psychiatry, University of Basel, c/o University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland; Tel: 004161 2657879; Fax: 004161 2654588; E-mail: Renata.Smieskova@upkbs.ch

complicated by the multidimensional nature of psychotic symptoms. Using specific functional paradigms, individuals suffering from schizophrenia manifested failure of some brain regions to activate to a task while other regions were over-activated [60].

3. STRUCTURAL AND NEUROFUNCTIONAL BRAIN-IMAGING FINDINGS IN ARMS

Over the past decade, structural magnetic resonance imaging (MRI) methods have been extensively employed to identify neuro-anatomical alterations in the pre-psychotic phases. Several techniques were implemented to investigate structural differences in ARMS individuals: voxel-based morphometry for gray [61-63] and white matter [64], region-of-interest analyses of hippocampal, cingulate and pituitary areas [65-73], cortical thickness [74] and pattern matching [75, 76], and gyrification index [77]. Overall, in subjects at high-risk for psychosis with subsequent transition to psychosis, as compared to the high-risk individuals without subsequent transition, MRI studies showed volumetric reductions in frontal, insular, cingulate, lateral and middle temporal, and cerebellar regions [13, 61-63, 66, 71, 75, 76, 78, 79]. These regions are similar to the regions of structural deficits found in first-episode schizophrenia [80-84] and in the relatives of schizophrenia patients [85, 86]. The latter indicates that the volumetric reductions in these regions are not only affected in prodromal or manifest psychosis but also represent potential vulnerability markers for the illness. Recent advances in psychiatric research indicate that neurocognitive deficits are also evident in subjects with an at-risk mental state (ARMS) [19, 87-90] and in non-affected first-degree relatives [91-96].

Functional MRI studies are based on known impaired cognitive domains in the early stages of schizophrenic psychosis. They use an 'activation paradigm', which engages the brain region/s of interest and the results reflect abnormalities in these specific cognitive domains. Some of the published fMRI and multimodal functional studies investigated neurofunctional abnormalities in ARMS [97-99] and found deficits in the frontal and temporal task-related networks [100, 101]. Several studies focused on functional deficits, while performing a working memory task [20, 97, 102, 103]. Such alterations cannot be attributed to the effects of illness or treatment and may represent markers of vulnerability to psychosis [100].

4. RESILIENCE FACTORS AND CLINICAL STAGING OF THE ARMS

Importantly, 90% of the ARMS individuals who made a transition to frank psychosis (ARMS-T) did this during the first two years after ascertainment [3]. After these two years, only further 3% of all included ARMS individuals developed frank psychosis, representing a 10-fold lower risk for transition as compared to the first two years after ascertainment (36% probability to transit) [3]. Similarly, a study by Yung confirmed that the vast majority of transitions occurred in the first two years (estimated hazard ratio 0.58) and significantly dropped over time (estimated hazard ratio 0.07) [104].

Some recent studies aiming to improve individual risk assessment showed that transition rate was declining over the past years [105, 106]. During the first two years, the transition rate declined from 31% published in 2003 [79] to 16% published five years later in a high-risk population [107]. The reasons for this decline are not completely clear. Most probably, individuals are more readily referred to early detection clinics than 10 years ago. Those identified as "at risk" might be less severely ill and therefore have a lower risk to rapid deterioration. Furthermore, the decline might be a result of non-pharmacological interventions, such as psychosocial intervention, family support, cognitive behavioral therapy (CBT) or other unknown (possibly protective) factors. Some ARMS individuals may have better internal resources, attitudinal approaches and overall functioning as seen by non-medicated schizophrenia patients [108]. They may recover subsequently [109]. Other indi-

viduals may be on the ARMS continuum for a longer period of time. The longer the subclinical psychosis persists in the general population over time, the greater the risk of transition to clinical psychosis as shown in a recently published 8-year cohort study [110].

A worldwide-accepted clinical staging model of psychotic disorders [1, 2] describes stages of ongoing psychosis with its characteristics and recommended treatment. Interventions according to the model should lead to prevention or delay of progression from earlier to later stages of disorder, and they should be chosen on a careful risk/benefit analysis [2, 111]. This approach can enable us to allocate each individual according to his/her deficits or abnormalities and to provide accurate intervention.

We postulate that those ARMS individuals, who are more vulnerable to transition and therefore have a higher probability for transition to psychosis, have less resilience factors and vice versa. Therefore, we suggest splitting the individuals with an ARMS according to the duration of their ARMS as well as according to their clinical outcome (Fig. 1). The first criterion focuses on the time span of risk: the short-term ARMS (ARMS-ST) group consists of ARMS individuals in a period shorter than two years after ascertainment; individuals, who are in ARMS continuum longer than two years belong to the second group (long-term ARMS, ARMS-LT). ARMS-LT individuals might represent a group with a vulnerability to psychosis but a relatively moderate or low transition probability [3]. All of the ARMS (ARMS-ST and ARMS-LT) still have to meet the PACE criteria and have not recovered in the meantime. According to the clinical outcomes ARMS individuals with subsequent transition to psychosis belong to the ARMS-T group. There were published several studies comparing ARMS-T and ARMS-NT (ARMS with no transition to psychosis) individuals (for review see [30]). ARMS-ST subjects are vulnerable to psychosis and we expect that around 30% out of them will transit (ARMS-T) in next two years, leaving still 70% of ARMS without transition to psychosis (ARMS-NT). The latter are of high clinical and research relevance and may be called ARMS-LT. We suggest following them longitudinally with the aim to investigate the course of their symptomatology and functioning as well as resilience factors protecting them from developing frank psychosis.

Thus the two ARMS subgroups (ARMS-ST and ARMS-LT) represent vulnerability groups to psychosis with different probabilities of later transition to psychosis. The ARMS-LT group might either recover, or develop psychosis or other disease, or remain on the risk continuum to develop psychosis. Still, according to the published data the ARMS-LT group has lower probability to develop subsequent psychosis than ARMS-ST. This interesting group could help us to define resilience factors in the at-risk mental state.

The spectrum of subsequent diagnoses and possible comorbid symptoms remains broad and worth to be studied further. Longitudinally followed-up groups of ARMS without transition give us an opportunity to better understand the trajectory of the disease process, when the vulnerability to transit is not subsequently followed by transition and when these ARMS individuals stay somehow protected. We are aware of inhomogeneity of this group and expect to detect broad spectrum of diagnoses or comorbid symptoms in a future. But probably, we can learn from these subjects, how to cope with their higher vulnerability to psychosis and still stay without transition.

5. NEUROIMAGING AND STAGING OF THE RISK FOR PSYCHOSIS

As shown in our recently published meta-analysis of neuroimaging predictors [30], there are known structural and neurofunctional deficits in ARMS individuals with subsequent transition (ARMS-T) as compared to the ARMS individuals without transition (ARMS-NT; see Table 1 summarizing data published in [30]).

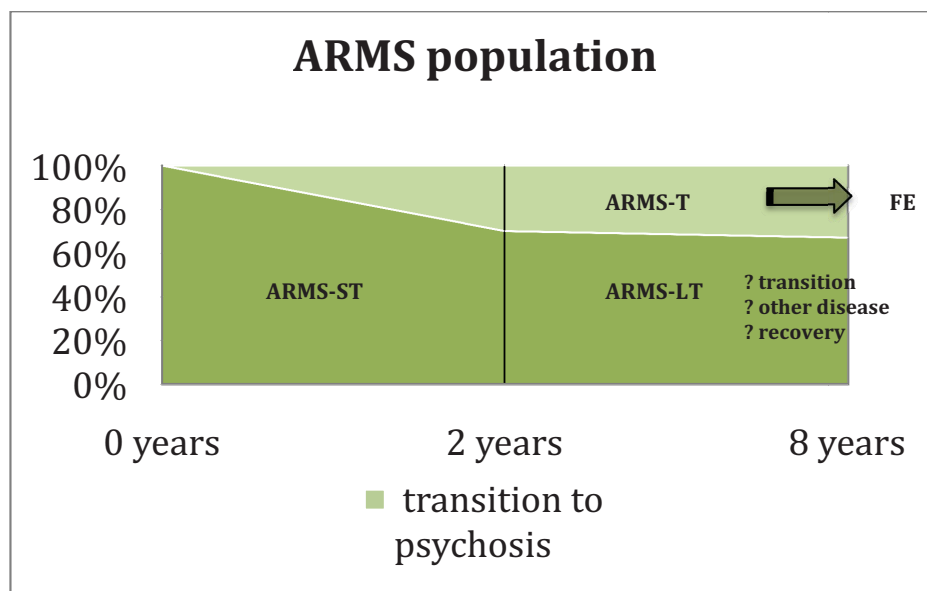


Fig. (1). ARMS population vulnerable to psychosis with descending transition probability in a time course of their at-risk state.

ARMS individuals can be divided according to the duration of their at-risk mental state into ARMS-ST (ARMS short-term) and ARMS-LT (ARMS long-term) individuals. ARMS individuals with subsequent transition to psychosis (ARMS-T) continue to first episode of psychosis (FE). ARMS-LT can be followed-up clinically and investigated for their vulnerability- and resilience-associated factors.

Later development of psychosis was associated with less GMV in the right insula, inferior frontal, and superior temporal gyrus [13]. Multimodal imaging analysis of structural and functional MRI during working memory showed association between BOLD response and gray matter in the right insula and middle temporal gyrus in all ARMS individuals [112]. ARMS-ST group had deficits similar to the ARMS-T group as showed our study comparing volumetric data of ARMS-ST and ARMS-LT groups [113]. Even more, these insular volumetric abnormalities correlated with clinical symptoms of psychosis [113]. The structural abnormalities in insular region have been described in individuals with impaired insight to the disease [114]. Positive relationship to the recovery and awareness of their abnormal experiences can be associated with increase in insular volume [115].

ARMS-LT with vulnerability to psychosis but lower transition probability might help us to find resilience-associated changes in their brain structure and function. We argue that ARMS-ST and ARMS-LT subgroups may contribute to the existing clinical staging model of psychosis.

6. CONCLUSIONS

Neuroimaging methods might in future contribute to the prediction of the probability for transition to psychosis and regarding the time course of illness. To be able to predict transition to psychosis as exactly as possible we should combine multimodal imaging approach with clinical symptoms and neurocognitive measures. In future, by improving the understanding of emerging psychosis, we may be able to selectively treat those patients with the highest risk

Table 1. Meta-analysis of volumetric and functional differences between ARMS-T and ARMS-NT (Modified from [30])

ARMS-ST vs. ARMS-LT / Region	Cohen's d (number of studies)*					
	Volumetric Abnormalities			Functional Abnormalities		
	Increased GMV	Decreased	No Change	Decreased BOLD	NAA/Cho	Decreased 5HT BP
Temporal cortex	0.1–0.8 (4)	0.3 (7)	(2)	-	Increased 1.0 (1)	-
Cingulate cortex	-	0.4–0.9 (4)	(2)	(1)	Decreased (1)	-
Prefrontal cortex	0.5 (1)	0.1–0.9 (10)	-	0.6 (1)	-	1.5 (1)
Cerebellum	-	(3)	-	-	-	-
Occipital lobe	-	-	-	(1)	-	-

* Numbers belonging to the affected brain region characterize range of effect size calculated as Cohen's d with the number of included studies in parentheses. When there is no Cohen's d, the effect size was not possible to calculate.

Abbreviations:

ARMS-NT - at-risk mental state without transition, ARMS-T - at-risk mental state with transition, BOLD – bold oxygen level dependency (fMRI parameter), NAA/Cho – N-acetylaspartate/cholin containing compounds (MRS parameter), 5HT BP – serotonin binding potential (PET parameter)

for psychosis. The treatment will be thus more efficient, selectively targeted and can integrate resilience-based non-pharmacological interventions to clinical psychiatry.

ABBREVIATIONS

ARMS	=	At-risk mental state
ARMS-LT	=	At-risk mental state long term
ARMS-NT	=	At-risk mental state without transition
ARMS-ST	=	At-risk mental state short term
ARMS-T	=	At-risk mental state with transition
CBT	=	Cognitive behavioral therapy
fMRI	=	Functional magnetic resonance imaging
GMV	=	Gray matter volume
MRS	=	Magnetic resonance spectroscopy
PACE	=	Personal Assessment and Crisis Evaluation Clinic
PET	=	Positron emission tomography
sMRI	=	Structural magnetic resonance imaging
WM	=	Working memory

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